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E D I T O R I A L

PRICES

IT is a wise person who adheres strictly to his field of specialization, and Economics is surely not this editor's field. On the other hand it would be difficult to conjure up a statement about high prices that would be any more misleading or inaccurate than some of those we read in the daily press, coming in many instances from those who are supposed to know.

Labor blames capital, capital blames labor. To some it is a Republican disease while to others it is a symptom of prolonged Democratic infestation. Economists to the left of center tell us its cause and cure while others on the right offer an almost opposite diagnosis and therapeutic regimen. Under these circumstances one is justified in stating his own beliefs if for no other reason than because every one else is doing so.

First we must record the fact that drug prices have not advanced to the same extent as most other commodities. There are many factors responsible for this but the primary ones are restraint on the part of producers and, most of all, a tremendously expanded production with increased efficiency sufficient to offset much of those influences tending to raise the price of the finished product. Many drug prices have steadily declined during the past few years because of such influences, the most notable being that of penicillin.

In the overall picture prices of many consumer items such as food, clothing, automobiles, etc. have doubled and still the price index seems to rise. What is the basic reason for this? Is it the mendacity of the merchant as some would have us believe? Not at all, for his greed is no greater than the laborer, the banker or the college teacher. It is human nature to ask what the traffic will bear. Some are just more favorably situated to ask than others and more likely to succeed in getting their price.

The primary cause goes back to this simple fundamental fact. During the war we made things to supply not consumer demand but to be *destroyed*. To make matters worse we did it on borrowed

money and paid our producers beyond that point where their earnings would be used up in living and taxes, permitting thereby accumulated purchasing power without goods and services to match it. The things that were made during the war—guns, tanks, shells and so forth are now either totally destroyed or totally disdained by the consumer. He wants food, clothing and shelter and he is determined to outbid his neighbor for the limited supply. Productive effort to supply these things is accompanied by further compensation so that the accumulated purchasing power is maintained.

This situation might have been avoided if during the war the government had taxed away all excess purchasing power. This policy, however, would have removed incentive and crippled production by the workers. We might then have lost the war.

Rationing and price control will not solve the problem since Americans are difficult to regiment during wartime and almost impossible to regiment in times of peace. Wholesale violations of such laws would lead to the same shambles which accompanied the eighteenth amendment and we have not yet recovered from its effect in encouraging disrespect for law and order.

There seems to be several sound approaches but none would make good political propaganda. First the labor movement in the United States must face the fact that the artificial levels in living standards made possible during the war cannot be maintained by any system or method and that a considerable retrenchment must be expected. The artificial standard accomplished during the war was done on borrowed money and further indebtedness on the part of the country could not long be continued. The American standard of living is high and it can be higher, but it must be accomplished by a process of orderly growth and not by the use of some magic formula in contradiction with all the laws of economics.

It is uneconomic for a laborer who is totally unskilled to make more than a college professor, and yet this is almost the rule today rather than the exception. The premium placed on certain workers during the war was justified for then they were more important than the teacher but they are not so today. Unless our society realizes this we can expect its disintegration for unskilled and uneducated people cannot maintain our social institutions.

Another approach is one in which all classes of our economic system can contribute—greater efficiency in production. If labor and

capital would discard many of the uneconomic practices in an honest effort to increase production without a proportionate increase in return great benefit to all would result. There is obsolete capital and there are inefficient methods of production. Union "feather-bedding" is all too common, as is the feeling that union can do no wrong. Capital has learned by hard experience that labor has a stake in production. Labor must not repeat the error made by capital years back in ignoring the other half of the production team.

Last but not least there must be a greater sense of social responsibility on the part of all Americans. It is high time our politicians consider truth more important than expediency, giving us leadership rather than chicanery. Whether we accept it or not every act we do influences others for good or for bad. In a society where each one thinks only of himself the end is most certainly anarchy and social collapse.

Americans need leadership; leadership that will tell the truth courageously rather than disseminate half-truths and encourage dissention between segments of our people for political purposes. America under such leadership needs to develop a team with every one of its citizens a member, each working and serving with the understanding that only through mutual cooperation and fair play can prosperity and happiness be attained.

L. F. Tice.

ANTISEPSIS AND DISINFECTION IN SURGERY*

By Edwin J. Pulaski, M. D., Major, M. C., A. U. S.**

Introduction

ALTHOUGH the application of drugs to wounds was practiced by the ancients, it was not until the classic work of Lister (43) that the full significance of bacterial infection in wounds was appreciated. Modern surgical procedures are based on Lister's observations that suppuration does not take place, provided access of bacteria from without is rigidly prevented. Oliver Wendell Holmes and Semmelweis, at an even earlier date, had concluded that puerperal fever could be prevented by aseptic precautions.

Lister achieved the elimination of infection from cases of compound fracture by the use of a crude carbolic acid, but not all attempts to prevent infection by this means were uniformly successful, and he later deprecated bringing this corrosive substance in contact with tissues (43).

Ever since the discovery by Pasteur of the bacterial etiology of infections many substances have been recommended for their antiseptic or disinfectant properties. Each year finds many additions to the list (40). In most cases these represent efforts to provide an ideal antiseptic.

Antisepsis and disinfection are far from being simple subjects and advances in our knowledge of the basic facts governing the action of antiseptics, together with changing concepts in the approach toward achieving sterilization of wounds, have added measurably to the complexity of the subject. The discovery of sulfonamides and antibiotics has been largely responsible for these developments and an enormous literature has accumulated on many aspects of the problem. Medical curricula, too often, are weak in presenting this subject in spite of its important bearing on surgery.

Many antiseptics are used today solely by tradition, a matter of habit, or because of current popularity. There is general misconception as to what can be done to bacterial flora in the tissues by

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these agents. Since many compounds are used to disinfect surgical instruments or excreta and act as protoplasmic poisons there are workers who consider all such agents in this category and therefore unsuitable for application to wounds.

In view of the many misconceptions relative to antisepsis and the plethora of statements regarding them, the author will try to present a review of the subject in a systematic manner in the following order:

1. Mode of action of antiseptics.
2. Need for antiseptics and disinfectants in surgery.
3. Those agents producing disinfection by physical means.
4. Antiseptics acting primarily by chemical activity, e. g., the "surface antiseptics."
5. Antiseptics which act by interfering with a specific function of the bacterium (sulfonamides and antibiotics).

Mode of Action of Antiseptics

The terms disinfection and sterilization are often used as synonyms. The accepted meaning is that after disinfection or sterilization an object contains no living bacteria, protozoa or fungi. Disinfection usually implies the use of chemicals to destroy microorganisms. Most disinfectants by reason of their nature are also destructive or harmful to tissues. Antiseptics are substances which in some cases kill bacteria and in others simply prevent multiplication, according to the character of the product and its method of use. Thus an ointment may be called antiseptic if it prevents the multiplication of bacteria but a mouth wash which remains in contact with the tissues for only a short time must actually kill bacteria to be so labelled.

Few substances are germicidal in body tissues so that the term disinfectant is reserved for agents used to destroy microorganisms in inanimate objects or on the intact skin while the term antiseptic is applied to those substances used to control infection in the body. The term chemotherapy was coined by Ehrlich and it is today accepted to mean the antiseptic use of a substance which inflicts maximal injury on the bacteria and minimal injury on the tissues of the body.

The ideal antibacterial agent would be one which was powerfully germicidal against all pathogenic bacteria in that bodily environment where its action was required but at the same time completely inactive against the tissues of the body. A number of other characteristics are highly desirable as follows:

Physical Properties—The substance should be in a form permitting rapid delivery and easy access to the area needed. Thus it must be soluble in tissue fluids well beyond effective levels and it must be capable of penetrating beyond tissue exudates to the site of the offending organisms. The vehicle in which it is applied must be inert and also release the drug in effective concentrations on contact with tissues.

Stability—The substance should be stable on exposure to light, air, temperature changes, humidity and transport.

Low Toxicity—It should lack any tendency to irritate tissue or to cause any adverse reaction on general administration.

Elimination—It should be easily removed from wounds or dressings when used locally.

Cost—The substance should be comparatively easy to prepare at low cost.

It is apparent that no single antibacterial substance so far available meets all these requirements.

For the proper selection of those agents suitable for the various needs in surgical practice it is necessary to understand the chemical, physical and biologic properties of the substances available. Laboratory tests have been developed to screen lethal tissue poisons from those wherein low toxicity warrants further study.

A number of factors are involved in antibacterial action. The potency of an antiseptic is usually expressed as its *phenol coefficient* which is obtained by dividing the maximum inhibitory dilution of the unknown by that of phenol. Information as to the minimum concentration in which an antiseptic will act *in vitro* is of value in that it serves as a guide for the selection of a concentration to be used in wounds. If a concentration greater than this minimum found effective *in vitro* is tolerated by the tissues the antiseptic may be successful. Other factors enter the picture, e. g., dilution by tissue fluids.

Thus phenolic compounds are greatly affected by dilution in their germicidal activity whereas the mercurials and the dyes are only gradually reduced in their activity by progressive dilution.

Time and concentration are interdependent and it is well known that if the concentration is increased less time is required for germicidal action. There is, however, a considerable variation in the speed of action between various antiseptics. The hypochlorites and peroxide are quite rapid as compared with the heavy metals and the sulfonamides, the latter being quite slow.

The temperature at which an antiseptic or disinfectant is employed is important, in that a high temperature increases the germicidal potency. This is particularly true in the case of the phenols. From the practical standpoint the use of an antiseptic at high temperatures is not feasible since the solution would either burn tissue or rapidly assume body temperature.

The susceptibility to the action of antiseptics in general varies with bacterial species. Spore formers and tubercle bacilli are quite resistant because of their impenetrability. *Streptococcus fecalis, Ps. aeruginosa* and other Gram-negative organisms possess considerable resistance to many kinds of antiseptics while gonococci and meningococci are easily killed. Many antibacterial agents show striking degrees of selective action on bacteria. For example, penicillin and gentian violet are strongly inhibitory to staphylococci but only poorly active against most Gram-negative organisms. Acetic acid, in a concentration hardly affecting most organisms, readily destroys *Ps. aeruginosa* which is to most substances quite resistant. A knowledge of selective action is imperative in the proper choice of an antibacterial agent for use against a specific organism.

It is well established that exposure of bacteria to sublethal doses of an antibacterial agent often results in the propagation of resistant and mutant forms that become increasingly difficult to kill. This factor has very important therapeutic implications such as the advisability of adequate dosage in the early stages of treatment and the change to another agent should habituation of the organism be suspected.

Antiseptics almost invariably are of greater value *in vitro* than *in vivo,* i. e., in the presence of body fluids or tissues. The organic matter with which the antiseptic comes in contact consists of plasma proteins, blood cells and foreign bodies such as sequestra

and necrotic tissue. These, in varying degrees, interfere with the antibacterial action. It is highly important to know how a given antiseptic behaves in the presence of such material and whether any appreciable antibacterial effect remains. All known antibacterial agents are toxic in some degree to tissues as well as bacteria but the toxicity for tissue varies greatly. A number of methods have been devised for testing tissue toxicity. Thus we have a determination of minimal lethal doses by intravenous, subcutaneous and intraperitoneal injection and the effects after application to the conjunctiva of rabbits. These methods establish the general toxicity of an agent according to the route of administration and the effects of absorption on contact with vital tissues. Such information is most essential for drugs to be administered systemically. When the antiseptic is to be used locally the effects on the skin, muscles, connective tissue and blood cells are of primary significance. The cells of these tissues can be studied histologically in experimental wounds or by tissue culture and the action on leukocytes determined by direct study in the presence of the antiseptic. The relative vulnerability of fibroblasts in tissues is unknown and it is not established that the behavior of one type of cell can be assumed to be similar to that of another type. Howes (34) has devised a very appropriate test for the determination of wound healing following the application of an antiseptic to similar wounds. By serial photographs he establishes the effect on the rate of epithelization in terms of change in the perimeter of an island of epithelium and the effect on the growth of the surrounding granulation tissue. Only by such data is it possible to evaluate accurately the relative toxicity of antiseptics unless they produce gross and immediate toxic effects.

The choice of the mode of application of an antiseptic introduces two problems: first, how can it be applied to an area so as to exert maximum results and, second, how can the substance be maintained in the area long enough to achieve the desired results. Aqueous solutions, as a rule, provide maximum antibacterial action but in such form solutions intended for the pre-operative preparation of the skin require a long time to dry. The use of alcohol as a vehicle produces more rapid evaporation and drying but otherwise it has no advantage. The case of phenol is interesting and it demonstrates the importance of the base or vehicle employed. Aqueous solutions containing 5 per cent phenol are highly toxic to

tissues but the same concentration in petrolatum is bland and non-irritating to wounds. Yet because of the greater affinity of the phenol for petrolatum than for water it is released so poorly from the base that the ointment is inert (52). Generally speaking, any vehicle other than water causes some loss in antiseptic power although it may be used to secure greater solubility, reduce toxicity or in some way to facilitate application. For immediate rapid effects an isotonic aqueous solution is preferable but for a more prolonged action a number of bases are recommended. For example, a Carbowax water-soluble base;[1] a vanishing cream type base;[2] or a lanolin type base.[3] To compensate for the slow release of antiseptics from these bases somewhat higher concentrations of the antiseptic must be included than is necessary in aqueous solution. Comparative data are needed to quantitatively express the rate of release of antiseptic from different vehicles in comparison with water (33, 36, 52).

From these considerations it will be seen that the "ideal" antibacterial agent has not been perfected. Although many compounds are antiseptic *in vitro,* each lacks some specific function or property that removes it from the "ideal" category. Thus one compound may be outstanding in speed of action while another may have outstanding penetrating power. For the complete evaluation of an antiseptic a multitude of tests is necessary and the results carefully considered. It must be determined what concentration can be used, how this is to be maintained and over what period of time the antiseptic must remain in the wound. Other considerations are the changes produced in the bacterial flora of the wound, the antiseptic's action on tissue repair (whether it is severely inhibited by organic matter) and the possibility of its producing drug resistance. Esthetic considerations such as staining, color, odor, etc., may be important (26). It is the stain produced by dyes which makes the use of these compounds unpopular.

These many variables are difficult to control and often data on each are not available. It is consequently not always possible to

[1] Carbowax is a trade name for a mixture of polyglycols sold by Carbide and Carbon Chemicals Corp., New York, N. Y. An excellent base may be prepared as follows: Carbowax (4000) 45 parts, propylene glycol 55 parts.

[2] A base of this type recommended by Jenkins may be made as follows: Oil Phase—Petrolatum, 48 cc., Arlacel C, 2 cc.. Aqueous Phase—Tween 80, 0.25 cc., Water q. s. to 50 cc. Arlecel C and Tween 80 are manufactured by the Atlas Powder Co. of Wilmington, Delaware.

[3] An excellent lanolin type base is sold as Aquaphor by the Duke Laboratory of Stamford, Conn.

establish or state definitely that one agent is superior to another. Manufacturers, by stressing some one point of superiority such as phenol coefficient or low toxicity, have introduced an enormous number of antiseptics on the market. It is apparent that some are superior to others and a clinical therapeutic test is undoubtedly the best criterion for selection provided that one's observations are complete and on a significant number of cases. One should also keep in mind the many variables which make up any group of "like" surgical cases as pointed out by Meleney (46).

Need for Antiseptics and Disinfectants in Surgery

Every surgical procedure requires some measure of disinfection and antisepsis to convert the non-ideal conditions to as near ideal as possible. Specifically, one tries to prevent the irreversible damage that is associated with the implantation of bacteria with resulting infection and to minimize the damage that ensues once infection has occurred. The surgeon should keep the following points in mind:

1. The oral cavity should receive pre-operative preparation when oral sepsis is present to minimize the risk of respiratory disease after inhalation anesthesia.

2. The microorganisms in the gastrointestinal tract should be destroyed or inhibited so that abdominal procedures will entail less risk of infection.

3. Infections of the lungs and urinary tract should be prevented or controlled when incident to or following surgery.

4. Wounds accidentally produced require prophylaxis. These are all contaminated and therefore potentially infected (3, 54). Such wounds often occur where ideal surgery is impossible because of such factors as time, geographical situation or anatomical nature of the wound. The need for antiseptics is increased under conditions of war as adjuvants to fundamental surgical steps such as debridement, control of hemorrhage and drainage.

5. Wounds in which bacteria have already gained a foothold and are producing an inflammatory process require appropriate treatment.

6. Methods for the destruction or inhibition of organisms which have travelled from a portal of entry by the blood or lymphatic

systems to other parts of the body (generalized infection) should be instituted immediately.

7. All sutures, tubes, drains, powders and solutions should be sterilized and all organisms contaminating knife blades, scissors, needles and the like should be destroyed.

8. Air in operating rooms should be sterilized and cross-infection eliminated in wards.

9. The microorganisms on the hands and arms of the surgeon as well as on the skin of the patient at the site of operation should be destroyed.

10. Contamination of gloves or hands after contact with infected material such as dressings should not be overlooked and when it occurs disinfection instituted.

Those Agents Producing Disinfection by Physical Means

Dry heat or hot air. Th. Paul has shown that bacteria dried at various temperatures, according to the organism, die partly as the result of an oxidation reaction. Desiccation is also partially responsible. Glassware and instruments which are not affected by loss of temper may be conveniently sterilized by dry heat. This is of value particularly when they should be dry in order to be stored for future use. Powders such as talcum, zinc peroxide, the sulfonamides and others which possess a tendency to cake on contact with water, oils and ointment bases may be sterilized by hot air at a temperature of 140° C. or over in order to destroy spores. The temperature is dependent upon the compound since too high temperatures will decompose some substances. A temperature too much above 160° C. will char cotton plugs and covers. A temperature of 140° C. for four hours for zinc peroxide and the carbowaxes has been found satisfactory (38). For the sulfonamides 145° to 150° C. for four hours is sufficient. Six hours at 140° C. are frequently necessary for petrolatum or mineral oil which act as protectives to the bacteria.

Moist heat. Moist heat sterilizes or kills bacteria by a completely different mechanism than does dry heat. The protein of the bacteria is coagulated by moist heat thus leading to quicker destruction. In the case of moist heat the thermal death points of the bacteria also

vary. Spores of certain bacilli and clostridia are exceedingly resistant and may live through 110° C. and 120° C. for ten minutes. In such cases it is necessary to heat for a longer period of time. This applies to boiling of instruments in water or the sterilizing of linens in a steam autoclave. In an autoclave the objects being processed become water-soaked but they can be dried by producing a partial vacuum as soon as the autoclaving process is finished. Ointment bases such as the carbowaxes act as protectives to the bacteria against moisture. In such cases the spores are not destroyed by steam sterilization.

Ultraviolet light. Ultraviolet radiation does not effect complete sterilization but rather a reduction in the total number of bacteria present. The radiations which destroy the bacteria are found in the spectrum from 2000 to 2950 Angstrom units and Finsen first treated skin tuberculosis with such ultraviolet radiation. These radiations destroy both pathogenic organisms and those causing decomposition and putrefaction (27) and they are particularly valuable in operating rooms where the effect is rapid. The incidence of operative and postoperative infection can be reduced by 50 per cent with the use of ultraviolet lamps. Cubicles for the handling of septic cases, nurseries, children's wards and similar departments may also employ ultraviolet radiation. Unfortunately protection against the erythema producing effect on the eyes and skin is necessary.

Antiseptics Acting Primarily by Chemical Activity (The "Surface Antiseptics")

Acids and Alkalies. It has been determined experimentally that maintenance of *p*H below 5 or above 9 for a specified period of time will allow for the establishment of a state of antisepsis (1). Except in the urinary tract the maintenance of such *p*H states is difficult partly because of the powerful buffering and neutralizing action of the tissues and fluids. In the urinary tract it is possible to maintain certain conditions of *p*H without harm to the epithelial lining. This is accomplished by the administration of mandelates, phosphates, ammonium chloride and similar substances. Mandelic acid is an effective urinary antiseptic.

The antiseptic activity of many acids is directly proportional to the hydrogen-ion concentration which they produce in aqueous solu-

tion. This is true also of alkalies in that their activity is directly dependent upon the number of hydroxyl ions which are produced. The theory has been advanced that acids and alkalies neturalize the free basic or acidic portions of protein and consequently destroy the bacterial organisms. Some acids exert their bactericidal effects due to the undissociated molecules. Among these are included acetic, lactic, benzoic, salicylic and mandelic acids.

The strong mineral acids which dissociate readily are not practical because of the fact that they irritate the skin and mucous membranes and are too caustic. Boric acid has been employed for years as a relatively non-irritating though weak germicide for the eyes and for burns. It is a cumulative poison when applied to extensive raw surfaces and since its antiseptic action is doubtful other agents would be more efficient (50). Superficial dog bites are sometimes cautérized with nitric acid although some believe it valueless since the rabies virus spreads so rapidly.

The organic acids are much less dissociated and therefore less powerful than the inorganic or mineral acids. Superficial *Ps. aeruginosa* infections are destroyed with weak solutions of acetic, lactic or propionic acids preferably in buffered solutions. These acids are also fungicidal. Buffered solutions of these acids are preferable in order to prolong the time of activity as well as their effectiveness. Experiments *in vitro* have shown that a weak solution of acetic acid requires 10 to 15 minutes to destroy cultures of *Ps. aeruginosa.* Thus it is clear that a vehicle is necessary to maintain the agent in longer contact and to inhibit neutralization by tissue fluids. A carbowax base containing 3 per cent acetic acid and 4 per cent sodium acetate is less irritating and possesses a more prolonged action than a 3 per cent solution of the acid alone (53).

It has been stated previously that maintenance of a high degree of alkalinity (above a *p*H of 9) is not conducive to the life of bacteria. Alkalies possess a solvent action in dissolving proteins and saponifying fats which property is of value in wounds if the agent is continuously applied. The Carrel-Dakin hypochlorite treatment is typical of this technique (43). Caution must be observed in such technique since too great an alkalinity is irritating and corrosive to the skin and other tissues (48). Repeated application of mild acids has been found less harmful in animal wounds than that of mild alkalies (35).

Alcohols. Absolute and 95 per cent strength ethyl alcohol are relatively ineffective. The greatest bactericidal power is obtained with a concentration of 70 per cent by weight. The activity is diminished considerably if this is varied (48). In 70 per cent strength only the less resistant bacteria are killed. The property of coagulating proteins which ethyl alcohol possesses in turn makes it locally toxic to tissues. Consequently, bacteria may be protected from its effect. Chloroform and ether will do the same. This coagulation of protein probably is the cause for the decrease in efficiency of other antiseptics when alcohol is employed as the solvent (24). Thus alcohol is not to be recommended in cleansing wounds of bacteria and dirt and greases. Experimental work has revealed that spores survive indefinitely in the presence of ethyl alcohol (38). Alcohol is commonly used to sterilize rubber caps of vials but when spore-bearing dust has accumulated such an agent is unreliable. Brief immersion of instruments in alcohol or wiping with an alcohol sponge does not guarantee sterility.

Ethyl alcohol is definitely of value in reducing bacterial flora after scrubbing. Hatfield and Lockwood (26) state "Through a modification of the Price technique by which the effectiveness of antiseptics *on freshly scrubbed* skin is evaluated, it is concluded that alcohol in strengths of 95 per cent and 70 per cent by weight is preferable to any group of commercially prepared agents specifically designed for skin sterilization."

Isopropyl alcohol, a wartime replacement for ethyl alcohol, is more bactericidal against the vegetative forms than is ethyl alcohol and the isopropyl is used in full strength (about 99 per cent) at which concentration it is most effective (48). The cleansing properties of isopropyl alcohol are better due to its lower surface tension. Since isopropyl alcohol is used in full strength it is less corrosive for surgical instruments because of the lower water content. Just as in the case of ethyl alcohol, isopropyl alcohol cannot be depended upon to kill spores. Routine use of alcohol is in the prevention of bedsores and decubitus ulcers, to harden the skin and minimize sweating in bedridden patients.

Aldehydes. The one aldehyde with significant bactericidal activity is formaldehyde. It is a gas, readily soluble in water and thus employed in aqueous solutions. Formaldehyde possesses an advantage over alcohol in that proper concentration it is effective against

spores as well as all forms of organisms. Its value lies in the sterilization of surgical instruments, gloves and excreta but its irritant and coagulant properties preclude its use on the body. A solution with a less objectionable odor than formaldehyde and one which does not corrode surgical instruments has been developed for cold sterilization of instruments by Tainter as follows: Isopropyl alcohol 1,000 cc., Oil of rose geranium 2 cc., Oil of cinnamon (or cassia) 4 cc., Distilled water 780 cc., Sodium nitrite 4 Gm., Triethanolamine 60 cc., Solution of formaldehyde U. S. P. 160 cc. This solution has been shown to destroy spores and is most reliable. Methenamine, forming aldehyde, is effective mainly in the urine since its action is to slowly release formaldehyde in acid solution. It is inert at the neutral or slightly alkaline *p*H of wound exudates.

Anionic and Cationic Types of Antiseptics (1, 2). The anionic antiseptics are the neutral or faintly alkaline sodium or other salts of acid of high molecular weight. The most familiar example of this type is common soap. The ammonium and calcium mandelates and the "acid dyes" such as acid fuchsin are also included. An enzyme system in the bacteria is interrupted by an interaction between the acidic ions of the agent and certain basic ions in the bacteria. A *p*H value more acid than blood is necessary for the reaction as confirmed by reports from the literature showing that anionic antiseptics have not been effective in wound exudates and only moderately effective as skin antiseptics. The use of mandelates in acidified urine is the only reliable application of anionics. Soap is commonly employed in surgery in the form of a lather, as a cleanser. Used in this manner it removes water-insoluble liquids by emulsification and solid particles of dirt and bacteria by suspension. Removal of particles is also aided mechanically by rubbing or brushing. Soap action varies with the fat from which it is made. The staphylococcus and colon bacillus are least affected by soaps but soaps have some germicidal powers against *Streptococcus pyogenes,* the pneumococcus, the gonococcus and *Treponema pallidum.* Soaps should not be relied upon to produce skin sterility. After mechanical cleansing it is necessary to eliminate the transient and resident bacteria. Mercuric iodide enhances the bactericidal property but certain disadvantages restrict its use. A promising new compound when incorporated with soap for the preparation of the skin in surgery is a synthetic phenol known as "G-11." Chemically "G-11" is 2,2′-dihydroxy-3,5,6-3′,5′,6′-hexa-

chloro-diphenyl-methane. Regular daily use of this compound in soap considerably reduces and maintains low bacterial counts (63). Cationic antiseptics act conversely to the anionic group by combining with certain essential acidic groups in bacteria to form non-ionized complexes. These essential ions which are probably nucleic acids are thus immobilized. Since the nucleic acids comprise 20 per cent of the dry weight of streptococci it is clearly shown how important this immobilization is. Included in this group are a large number of compounds which have one common characteristic, namely, they are salts of bases of high molecular weight and usually are hydrochlorides or sulfates. Included in this large class are the "basic dyes," such as brilliant green and crystal violet; the acridines, such as proflavine and 5-aminoacridine; and the quaternary ammonium salts exemplified by "Zephiran," "Phemerol" and "Ceepryn." Most of these compounds form neutral aqueous solutions. Several are colorless whereas others are highly colored since they are dyes.

The Dyes and Organic Bases. There are five classes under this heading. (1) The azo dyes, of which Scarlet Red is the best known. Scarlet Red is claimed to stimulate the proliferation of epithelial cells rather than act as an antiseptic. Its clinical value is a subject of controversy. Five per cent of Scarlet Red alone or with 0.5 per cent oxyquinolin sulfate in ointment form is employed to stimulate wound healing in burns, superficial wounds and chronic ulcers. (2) The acridines include acriflavine hydrochloride ("acriflavine"), proflavine hydrochloride, "Rivanol," and 5-aminoacridine, which is nearly colorless. The acridines possess an advantage in that their action is not seriously inhibited by serum. In strong concentrations they are bactericidal and in high dilutions bacteriostatic. The acridines are highly active against Gram-positive organisms and moderately so against Gram-negative organisms. Of this group proflavine and 5-aminoacridine are preferable since they are the least toxic to tissues. Their range of biological activity is similar. Proflavin is a yellow dye which requires a *p*H adjustment before use because of its acidity in solution. 5-aminoacridine, being nearly colorless, does not stain the skin nor the clothing and it is available as the neutral hydrochloride. These drugs possess an advantage over the sulfonamide drugs in that they are not inactivated by *p*-aminobenzoic acid nor are they inhibited by pus except for a mechanical interference. The British employ these useful antiseptics extensively in wounds and for

preoperative skin preparation [Bonney's paste (5)] since they are more active than the sulfonamides against *Cl. welchii*. A 1:100 proflavine-sulfathiazole powder spray is highly recommended for treating contaminated and suppurating battle wounds (45). Further trials should be carried out with these drugs. Solutions of the colored acridines must be stored in amber bottles due to their instability in light. (3) The fluorescein dyes include fluorescein alone and in combination with mercury, as for example Mercurochrome. Fluorescein stain possesses no antiseptic powers. It is employed as a diagnostic agent in the eye to determine corneal damage and intravenously with a Wood filter to diagnose the degree of burns; third degree burns appear black and second degree burns take on a yellow-green hue (14). Mercurochrome (24) is a comparatively weak disinfectant in neutral or alkaline medium. It has been much publicized as an all-purpose antiseptic. Early experiments gave startling results due to its use in acid media but further work has shown it to be weak in neutral or alkaline solution. Numerous experiments have shown that it can be condemmed on the basis of insufficient antibacterial power since it is incapable of sterilizing skin, superficial wounds or infected blood. (4) The basic dyes, which include crystal or gentian violet (6, 11, 48, 61) and brilliant green are widely used as surface antiseptics for which purposes they have been recommended. Both are bacteriostatic but not strongly bactericidal. They are selective in that they act particularly against Gram-positive organisms and are practically ineffective against Gram-negative bacteria. Species within species resistance is not uncommon. When employed in wounds the basic dyes coagulate proteins which forms an eschar under which the bacteria grow freely since the effect of the dyes is superficial. Infected wounds such as chronic ulcers, mucous membranes and serous surfaces have been treated with these dyes. Because the dye coating of burns delays skin grafting, masks cellulitis and erythema, and is expensive from the standpoint of soilage of linens and laundry cost it has been largely abandoned. (5) Methylene blue is feebly antiseptic. Its use now is limited chiefly to enhance visualization in the fistulous tracts such as the pilonoidal and anal.

Quarternary Ammonium Compounds (2, 7, 31, 58). Domagk, in 1935, shortly after introducing Prontosil, reported on the preparations known as the quaternary ammonium compounds. The first to be used in the United States was "Zephiran" which was followed by

"Phemerol," "Ceepryn" and others. They are cationics and also are surface tension depressants. This latter property causes water to foam when a small quantity of the agent is added and shaken with it. A wide variety of organisms fall prey to these agents which are rapidly bactericidal. Pus cells, tissue debris, blood and similar materials reduce their antibacterial activity. Areas which are first cleansed with soap must be carefully rinsed before use of these agents. Soaps, being anionic, i. e., bearing a negative charge, react with them and neutralize their effect.

The quaternary ammonium compounds are most advantageous in the preoperative preparation of the skin of both the surgeon and the patient (7, 31, 58). The tissue surfaces are well wet and penetrated by such agents due to their low surface tension, their detergent,[4] keratolytic and emulsifying action. In antibacterial activity they are comparable to tincture of iodine. The concentrations necessary for an antibacterial effect are relatively non-irritating. In one respect the surface activity of the cationics is a disadvantage. In repeated applications to wounds they disrupt tissue elements and cause hemolysis and their antiseptic strength is diminished by the protein present. The cationic detergents also are not very effective against spores (48). Surgical instruments may be sterilized and these detergents used for storage of sterilized instruments, providing their ineffectiveness against spores is kept in mind. Corrosion is prevented by addition of 0.5 per cent of sodium nitrite.

Halogens. No two chemicals possess as well known a reputation as active germicidal agents as do chlorine and iodine. Their reaction to form combinations with the protein amino groups is responsible

[4] Detergency is a phenomenon dependent in part upon the lowering of surface tension which likewise produces foaming. A large number of surface active substances have been introduced in recent years varying widely in their chemical composition. Such substances character characteristically possess a hydrophilic (polar) group or groups which likewise solubilize the compound and a lipophilic (non-polar) group. With part of the molecule having affinity for water and part being attracted by oil or air the molecule is capable of orienting itself at an interface whereby interfacial, *i. e.*, surface, tension is reduced.

Surface active agents are classified as anionic, which carry a negative charge, cationic which are positive and non-ionic which are uncharged. Soap and sodium lauryl sulfate are examples of anionic agents and the quaternary ammonium salts are the best examples of cationic agents.

Detergents by dispersing oils and adhering dirt from the skin greatly facilitate its cleansing and also assist in the cleansing of burned areas and in removing dressings. Most detergents are relatively non-irritating and some (the quaternary ammonium salts) are decidedly antibacterial in their action.

for their antibacterial activity. Continual application or constant renewal of applications is necessary since proteins rapidly inactivate them. The hypochlorite solution commonly known as Dakin's solution is usually employed in place of chlorine. As previously mentioned the alkalinity of the hypochlorite solutions is an additional advantage. As a result of the alkalinity they possess a destructive and solvent action on bacteria, pus, necrotic tissue, silk and catgut. The well-known Carrel-Dakin technique (9) of irrigation meets the necessary prerequisites of constant renewal. The disadvantages of this treatment are several: 1. Irrigations must be constantly renewed, special apparatus is necessary, and the daily change of dressings, even if painlessly accomplished, predisposes to recontamination of the wound from outside sources. 2. Surrounding skin must be protected (by petrolatum gauze), or bothersome irritations will occur. 3. An alkalinity of *p*H 10 must be maintained by buffers, because tissue irritation is marked on either side of this range. Thus the solution must be made daily and kept in dark bottles, because of its photolability. The next compounds to be considered, namely chloramine-T, Dichloramine T and Azochloramid, act more slowly and combine with organic matter less rapidly but their activity is more prolonged, particularly when serum proteins are present. Unfortunately they do not possess the effect on slough that Dakin's solution does (24). They are more stable but are photolabile and must be stored in amber bottles. The problem of Azochloramid in relation to wound healing was studied carefully by Anderson. Single applications for several days caused a reduction of the bacterial flora in granulating wounds but not in sloughing wounds. Healing time was not influenced in either type. In *in vitro* studies Azochloramid possesses a synergistic action with the sulfonamides but no proof has been advanced of this synergism in the body.

Iodine has had a wide reputation as an efficient germicide. It is commonly used in the form of the tincture and is one of the most reliable agents for pre-operative skin disinfection. The chief advantage of the tincture is the rapid drying brought about by evaporation of the alcohol. Although the tincture has been so widely used the aqueous solutions of iodine are gaining in prominence as more and more reports appear on their highly germicidal action. Lugol's solution, U. S. P., in a 1:6.4 dilution has been shown by Nye (49) to be active *in vitro*. For pre-operative skin preparation the aqueous

solutions possess certain advantages. Kraissl and Meleney (40) compared certain aqueous preparations (Ethiomine, Tetrodine) with Tincture of iodine, on guinea pigs. Addition of certain surface active agents to these aqueous preparations causes them to spread, penetrate, and dry more quickly than Lugol's solution. Where the tissues are abraded there is no stinging sensation as with the alcoholic preparations. The use of aqueous iodine preparations has been slow as a result of a necessity to choose between proprietary preparations.

There are available certain organic iodine compounds ("Chiniofon," "Vioform," "Diiodoquine") which possess no antiseptic value in their use as dusting powders on wound surfaces. Extremely low solubility is the responsible factor. Their use is limited mainly to that of amebicides (24, 48). The penetrating odor of iodoform has long been associated with antisepsis. However, its solubility in water or serum is so slight that it is practically inert. No confirmation has been presented that iodine is liberated by iodoform in contact with tissues. Thymol iodide (Aristol) possesses no value as a local antiseptic for its solubility in water is still less.

Heavy Metal Salts and Compounds

Mercury. Cells contain sulfhydryl (SH) groups which are coagulated by inorganic mercury salts to form mercury proteinates. Functional enzyme systems are inactivated and deprived of nutritional support by the compound formed. The reaction is reversible and under optimum conditions the proteinate is dissolved and the bacteria are free to resume normal activities. The bacteriostatic action of the mercurials therefore is diminished considerably by the presence of skin, blood and wound exudates which contain sulfides and sulfhydryl groups. In addition the simple mercuric compounds are irritating and toxic and not safe for use in wounds. Mercuric chloride solutions which are acid in reaction are very slow in their antibacterial action. This coupled to the fact that a small quantity of soap inactivates a whole basin of the solution is a drawback to their use as hand rinses. Sterilization of instruments with these compounds is precluded because of their corrosive action. In the disinfection and storage of mechanically clean catheters, bougies, filiforms and similar instruments where there is no danger of spore contamination a 1:1000 solution of mercury oxycyanide is used. Germicidal activity of soaps has been increased by incorporation of alkaline potassium mercuric iodide. The flora of the skin is not appreciably reduced

by this compound or mercuric chloride but strangely a "sterile" cutaneous surface may be produced. Price (51) explains this as due to the transparent film on the skin under which the bacteria are confined. Multiplication occurs under this film. The bacterial flora present double every 50 minutes. Sweating breaks the film and the uninjured bacteria are released.

Merthiolate, a complex organic mercurial, and Metaphen, a phenyl mercuric compound, and related agents do not take a very clear position. They do not liberate readily inorganic mercuric ions but they possess cations of high molecular weight which opens the possibility of their behavior as cationic antiseptics. Compared with the simple mercury compounds their potency is much greater, but their toxicity and irritating power are considerably less. In the presence of serum proteins they retain a fair proportion of their activity but blood and pus inhibit their activity to some extent. They are not suitable for wounds and are not as efficient as is commonly believed for the disinfection of instruments (6). As preoperative skin disinfectants they are widely used. Their slow action (slower than iodine) and their lack of sporicidal action are disadvantages. Johnson (37) has found that Merthiolate is unreliable as a preservative for stored liquid plasma.

Silver. Silver foil. Metallic silver is bactericidal and is economically practical in the sterilization of water. Very little evidence has been accumulated in favor of the insertion of silver foil into wounds as an application of the oligodynamic action of metals. A compound of silver, namely the nitrate, is employed in surgery mainly for cauterization. It is also of use in trimming of granulation tissue, warts, etc. Corrosion, astringency, pain and irritation accompany its application. Silver nitrate formerly was used with tannic acid in the treatment of burns. This has been discontinued because it increases the depth of the burn, masks cellulitis and infection, and delays wound healing and early skin grafting. Colloidal silver compounds provide antisepsis by the release of very low concentrations of silver ions. In addition, they are non-corrosive and relatively non-irritant. These compounds are employed mainly on mucous membranes. Argyria, an irremediable discoloration of the skin or mucous membrane, may occur as a result of the use of silver for a long period of time. Solutions of silver should be freshly prepared as they are photolabile.

Bismuth. Mechanical protection of inflamed or irritated surfaces is provided by the insoluble bismuth compounds. Antiseptic action is possessed by certain combinations of phenols and bismuth salts in which the hydrogen in the benzene ring has been replaced by bromine or iodine such as bismuth tribromphenate (Xeroform). This compound is recommended by plastic surgeons to cover areas of skin grafts and donor sites (66). No delay in wound healing has been observed under this dressing. Xeroform is applied in ointment form for which the formula is: Bismuth tribromphenate 3, petrolatum 95, paraffin 1, beeswax 1. Several layers of narrow mesh gauze in a rectangular tin box are impregnated with the ointment and the whole sterilized in the oven at 140° C. for 4 hours.

Oxidizing Agents. The oxidizing agents act against bacteria by oxidation of the protoplasmic constituents. Included in this group are ozone, the permanganates and peroxides. Agents of this type are particularly effective against anaerobic organisms which are inhibited by a high concentration of oxygen. Proteins inactivate these oxidants and no distinction is made between those of bacteria and of tissues. They must be constantly renewed in order to sterilize unless the effect is instantaneous. Zinc peroxide (U. S. P. medicinal grade), recently introduced, is the only peroxide which has prolonged action.

The powder may be employed as a 40 per cent cream made with sterile water or a 20 per cent ointment made with a carbowax base (55). Both must be freshly prepared. In these vehicles the zinc peroxide will slowly liberate oxygen in a wound for 24 hours. *In vitro* tests have shown this chemical to be bactericidal to sporulating anaerobic Gram-positive bacilli, hemolytic streptococci and pneumococci, anaerobic cocci and bacilli; but not to the staphylococcus or most aerobic Gram-negative rods. Many uses have been developed for zinc peroxide in surgery among which are included the following: 1. orally as a mouth rinse and gargle in Vincent's angina and pyorrhea alveolaris; 2. topically, on foul-smelling, indolent wounds such as ulcerated cervical cancers which are covered by sloughs produced by Gram-negative anaerobic non-spore forming bacilli such as *B. fusiformis* and *B. necrophorus;* 3. in conjunction with excision and wide exposure for control of the chronic indolent burrowing ulcers caused by a microaerophilic hemolytic streptococcus (48); 4. in conjunction with excision of devitalized tissues and wide

exposure for control of the spread of bacterial synergistic skin gangrene caused by the symbiosis of two or more organisms (48), 5. in empyema after evacuation and rib resection where anaerobic mouth organisms are located on remaining fibrin and adherent slough; 6. around colostomies as a dressing, in the perineum after prostatectomies and resections, and in the anal canal after hemorrhoidectomies and fistulectomies (8). Zinc peroxide does not reach the deep and widespread infiltration of the infection therefore it does not have a material influence on gas gangrene unless the exposure is adequate. Zinc peroxide decomposes into zinc oxide and hydroxide which remain in the wound and provide a disadvantage. In rectal cases their astringency is advantageous. The vehicles in which zinc peroxide is suspended are absorbed or washed away by exudates which causes the chemical to dry. Therefore the wounds should be protected by over-layers of water-saturated cotton and several thicknesses of petrolatum or zinc oxide ointment gauze. Although hydrogen peroxide is a weak antiseptic it does have some value in surgery as an aid in releasing sticky exudate soaked dressings, cleansing surface wounds and like conditions. A mixture of hydrogen peroxide with Tincture of green soap is useful in removing crusts and dried wound exudates. The concentrations necessary for potassium permanganate to be effective are irritating and therefore it is no longer recommended.

Phenols and Phenolic Derivatives. Phenol is the simplest of this group of antiseptics. It is soluble to the extent of approximately 6 per cent in water. Because of its great destructiveness to tissues its use in surgery is limited chiefly to opening furuncles by allowing the phenol on a needle or toothpick to puncture the center of the furuncle and simultaneously seal off the capillaries (bloodless technique). Although more bactericidal and less toxic, the higher phenolic derivatives are less soluble in water. The cresols, of which Lysol (a mixture of ortho-, meta- and paracresol) is best known, must be dissolved by means of soap in order to be effective. Lysol is three times more bactericidal than phenol and slightly less toxic but its caustic property renders it unfit for wound or skin applications. Lysol is chiefly used for the disinfection of contaminated utensils and the scrubbing of walls, floors and bath tubs. Cresols, unfortunately are not sporicidal; not very soluble in water; possess a strong and persistent odor; and lose germicidal activity when mixed

with too much soap. Hexylresorcinol, rejected by the Council of Pharmacy and Chemistry in 1936 as an antiseptic for the N. N. R. but official in the U. S. P. as an anthelmintic, is highly bactericidal under optimal conditions. It is irritating to tissue and its activity is diminished by organic matter. Thymol is fungicidal and has produced varying results in the treatment of actinomycosis, blastomycosis, moniliasis and coccidiodal granuloma. Trinitrophenol, commonly known as picric acid, is not so widely used as a burn dressing and for preoperative preparation of the skin as formerly because of the fact that it is a systemic poison and occasionally causes a severe local dermatitis. A valuable disinfection with a low toxicity for use on inanimate objects is a combination of certain synthetic alkyl and halogen phenolic derivatives known as amphyl. Moderate amounts of organic matter do not inactivate it. Pulaski and Meleney (54) found para-chloro-phenol to be most effective against *Ps. aeruginosa* and *Proteus vulgaris* in dilutions of 1:3000 to 1:5000 both *in vitro* and also in the control of superficial and adequately exposed wounds infected with these organisms. A concentration of 0.25 per cent in carbowax base applied once daily is recommended.

Comment

The many antiseptics that have been presented represent the continued efforts throughout the years to improve surgical antisepsis. Their acknowledged failure as "all purpose antiseptics" has resulted in widespread pessimism concerning their utility in practice. Two quite opposite trends have developed: first, there are new antiseptics constantly being introduced and used; second, a trend has developed which might be termed "antiseptic nihilism"; it discredits all antiseptics for use in wounds and recommends the use of agents to stimulate the normal mechanisms of the body in combatting the infective process. According to this school of thought only heat and salt solutions (lymphagogues) should be used, as sodium chloride, sodium sulfate and magnesium sulfate.

Is it not too much to ask that all the requirements of the "all purpose antiseptic" be met by a single substance? It is certain that up to the present no chemical has been discovered which effectively combines all of the properties demanded of a general antiseptic although a considerable amount of time has been spent in search of it. At present the all purpose antiseptic appears to be an impossibility.

For many years clinicians and investigators have had a fixed idea concerning a "general purpose antiseptic" and this idea has been perpetuated by pharmaceutical houses in their advertising. The term itself suggests that there are substances effectively antibacterial against all forms but still sparing the body tissues. Such generalities should be succeeded by the choice of specific substances which perform the best for a specific requirement which is in essence the concept of chemotherapy. By such means one selects agents having a much greater affinity for the bacteria present than for the tissues of the host so that the microorganisms can be overwhelmed at minimal expense to the surrounding tissues. It has been pointed out how certain agents can be used with maximum advantage against certain organisms, i. e., they are chemotherapeutic while others are so damaging to tissue that they can only be used on non-living matter.

The "physiological school" also falls into similar errors as those who believe in an "all purpose antiseptic" by limiting therapy to heat and saline solutions, whether passive (isotonic) or active (hypertonic). Although the use of hypertonic salt solutions can hardly be called physiological, both methods commit the same error in disregarding the bacterial flow of the wounds. In their place these methods, like a given antiseptic, have value but not universally so.

Antiseptics Which Act by Interfering With a Specific Function of the Bacterium (Sulfonamides and Antibiotics)

In previous sections those agents which act as antiseptics when locally applied have been discussed. In this section will be discussed those agents which control infection by what might be called systemic chemotherapy. There are many more possibilities for the use of agents of this type than for the others. Chemotherapy by means of the circulation began centuries ago with the treatment of syphilis by mercurial inunction. It has progressed through the ages to the sulfonamides and antibiotics for treatment of bacterial infections.

Ehrlich and Shiga in 1904 used trypan-red, a synthetic dyestuff, to cure an acutely fatal general infection in mice due to trypanosomes. Quinine was the only substance ever used before in an analogous manner. Behring's successful use of antitoxin in diphtheria was valuable but serotherapy still did not furnish a universal method of treating bacterial diseases. This coupled with the fact that a syn-

thetic organic compound had cured a protozoal infection furnished the incentive for research. Examination was made of the aniline dyes. Gentian or crystal violet was shown by Churchman to have powerful action. Morgenroth and his associates reported that optochin (an alkaloid of the quinine group) had cured mice whose blood was infected with virulent pneumococci. In the untreated controls a rapidly fatal septicemia occurred. No similar effects had been achieved with any other drugs or organisms in other animals. Antisera, antitoxins and bacteriophages were introduced but the situation was still not very hopeful.

A. Sulfonamides (60)

Domagk (15) in 1935 announced that hemolytic streptococcal sepsis in humans as well as in mice could be controlled by treatment with certain azo dyes. No announcement of any chemotherapeutic agent was ever so startling or so immediately effective in saving so many lives. Sulfanilamide was discovered to be the active part of the dye molecule. The new age of chemotherapy which the discovery heralded has led to more fundamental progress in antisepsis as well as the solution of many problems of therapy. The search for new agents has become more rationalized. The sulfonamides act systemically by confining their action to a specific function of the bacterium rather than a universal chemical effect employed by the antiseptics discussed in previous sections.

As a result of certain inherent characteristics information on the sulfonamides was rapidly accumulated. Inexpensive manufacture and general use resulted from their comparative chemical simplicity and feasibility of synthesis. This latter factor showed the way for the preparation of many derivatives of the original compound. *In vitro* study is possible since the sulfonamides do not require the natural defense of the body for their effect. Not only do they dissociate as acids but the presence of an amino group which can be rapidly diazotized allows for accurate and fairly simple colorimetric tests of concentrations in the body fluids. Thus the calculation of therapeutic levels is expedited. The mode of action of the sulfonamides is much less definite than are their therapeutic properties and their limitations due to toxicity and infectiveness against certain type of organisms. The discovery (67) that *p*-aminobenzoic acid neutralizes the effect of sulfonamides on hemolytic streptococci *in*

vitro and *in vivo* led to the conclusion that these drugs must displace or block the utilization of an essential metabolite, probably *p*-aminobenzoic acid, from a bacterial enzyme. With this enzyme system no longer able to function the organisms could not utilize food material and were unable to survive. Thus the fact that the sulfonamides attack a specific function of bacteria was established. This was one of the first successful attempts in the establishment of antisepsis by this method and proved of great biological interest (13).

Phagocytosis has always been an important factor in eliminating infectious organisms from the body. The sulfonamides allow the host to act against the organisms which is a *secondary* factor in their activity.

Unfortunately there are substances of importance to the surgeon which also inhibit sulfonamides. Procaine and other related local anesthetics are esters of *p*-aminobenzoic acid. When injected they decompose into the parent compound. Inhibiting substances are also present in peptones, pus and necrotic tissue.

Bacteriological diagnosis, proven efficacy, pharmacological properties, and toxic reactions (variety, frequency and severity) are the factors to be considered by the surgeon in choosing a sulfonamide compound for control of surgical infections. Sulfadiazine is the best drug for infections caused by hemolytic streptococcus, pneumococcus, meningococcus, Friedlander's bacillus and also in *B. coli* and other sulfonamide sensitive urinary tract infections. In gonococcic infections sulfathiazole and sulfadiazine are preferable. Sulfasuxidine takes precedence in bacillary dysentery and preoperative reduction of the Gram-negative flora of the intestine. Hemolytic *Staphylococcus aureus,* the enterococcus and the viridans group of streptococci are comparatively unaffected by the sulfonamides. Sulfonamide therapy is ineffective against anaerobic and microaerophilic hemolytic streptococcus infections irrespective of location. Gas gangrene is not prevented nor is its course influenced by the sulfonamides. They are of little value in brucella, pasteurella, and hemophilus (influenzae) infections.

The local treatment of some bacterial infections by means of crystalline sulfonamides has attained widespread use following the report of control of infection in compound fractures by Jensen, Johnsrud and Johnson. Colebrook found sulfanilamide valuable when topically applied to superficial open hemolytic streptococcal infec-

tions. As a result of lay publicity on the control of infections in war wounds the sulfonamides are enjoying popularity as general purpose antiseptics. The local use of sulfonamides has been carefully investigated. When used to greater extent than a dusting of soluble sulfanilamide they may cause irritation, produce exudate, delay healing and promote the formation of adhesions. Inhibition by necrotic tissue and pus is pronounced. Rapid absorption and toxic blood levels result from the application of more than 10 Gm. over extensively wounded or burned areas in a 24 hour period. When continuously applied to intact skin for more than five days sensitization may occur. This is exceedingly dangerous since it may prevent the use of the sulfonamides later in an infection against which no other drug is effective. These factors are serving to reduce the local use of sulfonamides for wound antisepsis. It is now felt that local use of sulfonamides in wounds has no advantage over systemic administration of the drugs.

Drug Resistant Infections

It has been observed in a certain proportion of cases of pneumonia, wounds, burns, meningitis, gonorrhea, etc. that the sulfonamides do not control the infection. Worthy of particular mention are those refractory cases which obviously have the same species of causal organism and clinical features as the responsive ones. Such organisms are believed to be drug resistant. The infection first is affected by the drug but before it can be controlled the organisms develop resistance. The resistant bacteria in turn propagate resistant bacteria. They still retain their virulence. Variance in defense by the host also plays a part but this cannot be measured readily. *In vitro* testing of the responses of each patient's strain of organisms to sulfonamides has been developed into a simple technique (25). With this test accurate prognosis of results can be made and the period of time wasted before recognition that other forms of therapy are necessary is decreased. This *in vitro* testing promises much for the future for in some infections (fulminating) life is dependent upon the early use of the proper drug.

B. Substances of Biologic Origin

Nature is a treasure of antibacterial agents. Quinine, emetine, chaulmoogra oil, tannic acid and many others are plant products.

Even cabbage, onion, barberry plants and others have provided extracts which possess bacteriostatic agents. Chlorophyll has been found of promise in the acceleration of wound healing (59). Many of these substances require further investigation. Selective antibacterial properties are found in substances contained in tissues and body fluids.

Toxins, antitoxins and immune sera come from animals. The prophylaxis of gas gangrene with such products is not as clear cut as immunization in diphtheria and tetanus. The specific antibody still retains an important position in the prophylaxis and treatment of bacterial infections. In infections of the gas gangrene and *Clostridium tetani* group bacteria are so actively toxigenic that penicillin and the sulfonamides have very little direct neutralizing effect upon the toxin.

1. Antibiotics. Bacteria and fungi recently have attained great prominence as sources of chemotherapeutic agents. Seven groups of microbial products produced from an amazingly large variety of unrelated microorganisms have been listed by Waksman. (64) Included in this listing are polypeptides such as tyrothricin, pigments such as pyocyanin (alphaoxyphenazine), lipoids, such as pyocyanase, organic bases such as streptothricin, simple organic molecules such as hydrogen peroxide, and others, such as penicillin. In general the antibiotics are toxic to animal tissues just as are the synthetic chemical compounds. Many antibiotics have been isolated but only the following four show therapeutic promise: tyrothricin, penicillin, streptothricin, and streptomycin. The N. N. R. has approved the first two. The use of pyocyanase in the local treatment of infections has been discontinued or limited due to its instability, variability of organisms from which it was derived, and lack of information on the conditions controlling its formation.

a. Tyrothricin. Dubos (17) in 1931 first extracted tyrothricin from cultures of *Bacillus brevis,* a Gram-positive, aerobic, spore-forming, soil organism. To this worker should go the credit for renewing the interest in antibiotics. Tyrothricin is a protein (polypeptide) and a hemolytic agent which makes it dangerous if given intravenously. It is ineffective intravenously and orally as well. It consists of at least two substances, gramicidin and tyrocidin. Gramicidin is more active and although hemolytic is relatively non-toxic

for other tissue cells. Several species of Gram-positive organisms such as pneumococci, streptococci and staphylococci are susceptible to its action. It is of value in mastoiditis, burns, empyema, superficial ulcers, and similar conditions where direct contact locally can be accomplished. Its limited penetrating powers restrict its use in deep-seated infections. Tyrothricin inhibits enzymatic action in the bacteria causing a retardation of growth and lysis of cells. Saliva, urine and serum do not inhibit it to any degree. It is greatly inhibited by Gram-negative bacilli which in mixed infections may even protect the sensitive Gram-positive bacteria.

b. Penicillin. Penicillin is a solid substance extracted from broth cultures of the mold, *Penicillium notatum*. The sodium and calcium salts are the forms principally used. Fleming discovered the presence of penicillin in 1929 but it was not applied clinically until Chain and others produced it in sufficient quantity.

Penicillin is a yellowish-brown powder and is marketed in sealed ampules. It is unstable in air, hygroscopic and loses potency rapidly when exposed to heat, alkalies, acids, primary alcohols and oxidizing agents such as hydrogen peroxide. Crystalline sodium penicillin, just recently released, is much more stable and can be stored at ordinary temperatures without refrigeration. It is believed that some of the impurities which cause reactions in some patients have been eliminated in this product. Penicillin is extremely soluble in water, saline, and dextrose solutions. The potency of penicillin preparations is measured by comparing them with a standard using either the serial dilution method or a modified agar cup technique and a standard strain of organisms.

In penicillin therapy it is necessary to know the infecting organism. Gram-positive cocci and bacilli, spirochetes, gonococci, and meningococci are very susceptible but Gram-negative bacilli and acid-fast bacilli are resistant. Enzymes (penicillinases) produced by Gram-negative bacilli and by certain aerobic Gram positive spore bearing bacilli such as the *B. subtilis* group inactivate penicillin. It is also rapidly inactivated by certain strains of resistant micrococci. Infections due to pure cultures of susceptible organisms are considerably more affected by penicillin than are those due to mixtures of Gram-negative and Gram-positive organisms. Penicillin is the least toxic of all known antibacterial substances. Reference was made to resistant strains and acquired resistance under the sulfonamide drugs.

These factors are also prevalent in penicillin therapy but to a lesser degree.

Penicillin possesses certain advantages over the sulfonamides. It is less toxic and therefore there is no tendency to cause the side effects observed with the sulfonamides. Large numbers of bacteria, blood, pus, peptones or necrotic tissue products do not inhibit it when applied locally. In local administration it tends to diminish the exudate rather than increase it. Drug-fastness or resistance is less frequently observed. Unfortunately it does possess specificity of action; is inhibited by Gram-negative bacilli; and is rapidly absorbed and excreted, making frequent dosage necessary. Instability was initially a disadvantage but this had been diminished to a considerable extent.

Oral administration of penicillin in conjunction with alkalies and other compounds has been accomplished and provides a simpler method of maintaining bacteriostatic levels (18). By this oral route several times the parenteral dosage is required to maintain adequate blood levels.

Penicillin is also administered locally or systemically. Parenteral administration for common infections requires a dosage of 100,000 or more units daily, divided into three-hour doses. For topical use solutions or ointments containing 500-5000 units per gram are recommended. Daily instillation of 10,000 to 20,000 units diluted in from 5 to 10 cc. of spinal fluid or in 10 cc. of isotonic saline solution is the average dose by intrathecal administration. Two or three times this dosage and volume are necessary for inthrathoracic instillation. Peanut oil or oil and wax suspensions of the penicillin are used to slow absorption on intramuscular injection. For topical application penicillin powder with dry plasma, or incorporated into an ointment base such as carbowax or purified lanolin, provides a preparation from which the medicament is slowly released.

Claviformin, clavacin, penicillic acid, pyocyanin, fumigatin, streptothricin and streptomycin are also antibiotic agents which have been developed with a view to finding an agent which is less specific. Streptothricin and streptomycin are the only two which have shown clinical possibilities.

c. Streptothricin. This substance is obtained from *Actinomyces lavendulae*. It showed promise in the early days in the local treat-

ment of infected wounds and burns and in those infections produced by dysentery and Salmonella organisms (Gram-negative bacterial infections). Its activity is not influenced by blood, serum, peptone or B complex vitamins and is not destroyed by gastric acidity. However, it has been more or less overshadowed by streptomycin.

d. Streptomycin (20, 29, 30, 39, 56, 57). This substance was first isolated in 1942 from two strains of Actinomyces related to *Actinomyces griseus*. It is soluble in water and possesses a selective action against Gram-negative bacteria as does streptothricin but it is considerably less toxic. Streptothricin possesses some effect on fungi which streptomycin does not. Experiments with *in vitro* tests and infections in mice have shown that streptomycin is active against a variety of Gram-negative and positive bacteria. Streptomycin possesses an effect therefore on such Gram-negative organisms as Eberthella, Salmonella, Escherichia, Shigella, Klebsiella, Brucella, Pasteurella, and Proteus groups. Considerable resistance is shown by some strains of Pseudomonas. Sensitivity to streptomycin is shown by staphylococci, hemolytic streptococci and pneumococci whereas resistance is exhibited by all members of the spore-bearing, anaerobic group. Streptomycin is more effective when parenterally administered. Orally, sufficient dosage will sterilize the gastro-intestinal tract of lactose fermenting organisms. In order to maintain an effective blood level streptomycin must be injected frequently since it is rapidly excreted by the kidneys. The average daily dose administered intramuscularly is one to three million units divided into three hourly periods. Streptomycin is indicated in tularemia, influenza, and *K. pneumoniae* infections and as a supplemental aid in peritoneal and urinary tract infections caused by susceptible Gram-negative and positive organisms. It has shown some promise in tuberculosis therapy.

Lysozyme (16, 32), a polypeptide is obtained from tissues and egg white. It destroys a polysaccharide structure of susceptible bacteria. It is possible that other enzymes will exhibit valuable properties in surgery not for their antibacterial activity but because they accelerate digestion of necrotic tissue which provides the greatest inhibition to antiseptics. The bacteriophages were introduced long before the sulfonamides and penicillin. They were used in treating

B. coli, B. proteus, Staphylococcus aureus infections and bacillary dysentery. Further investigations of these may reveal new possibilities.

It is with these substances which act by interfering with the essential metabolism of certain organisms that the greatest developments of the future must lie.

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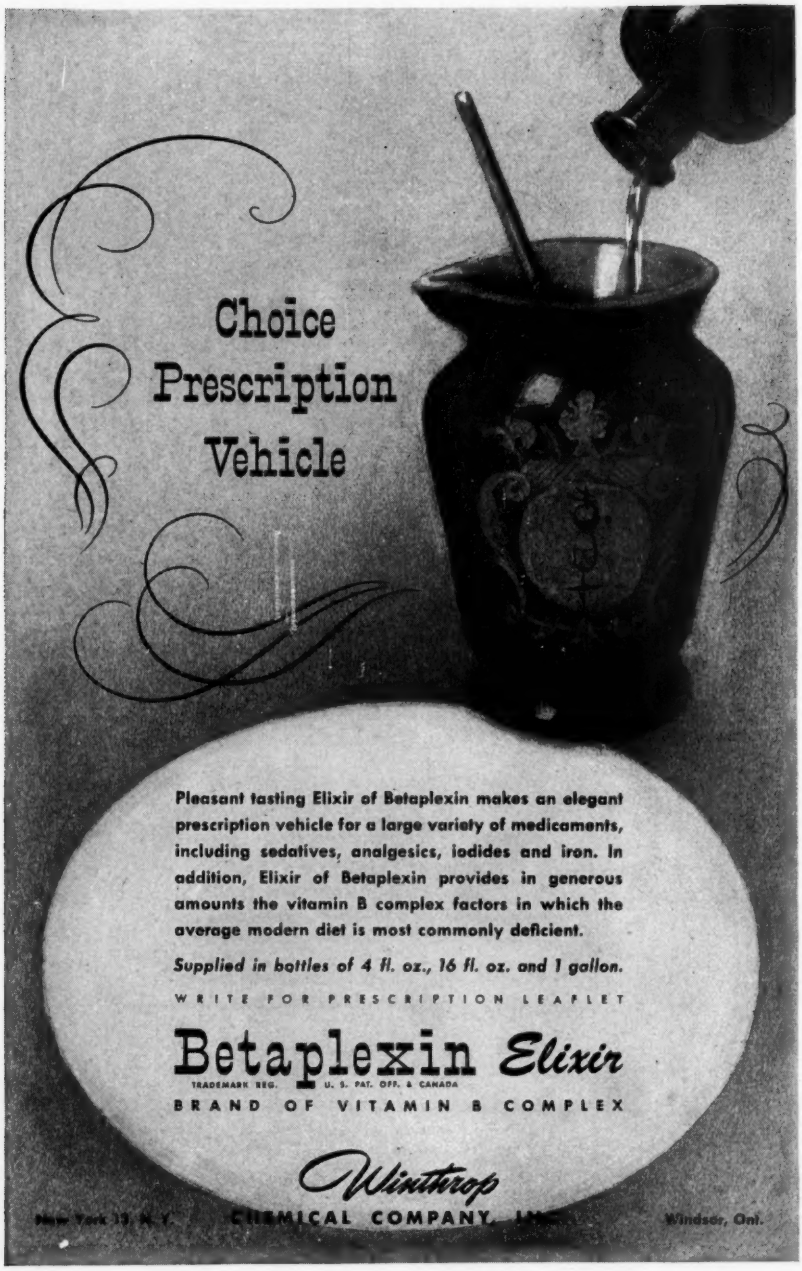
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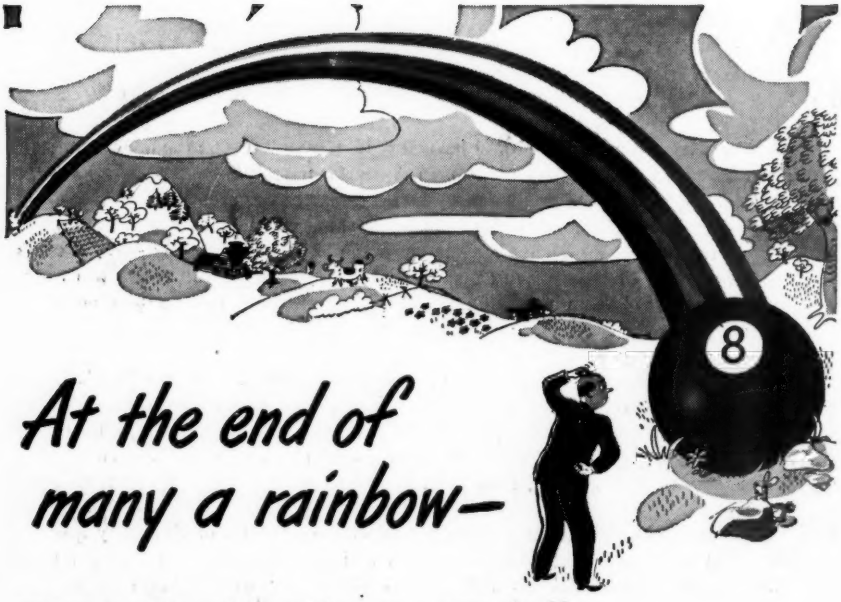

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